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Sensorimotor gating deficits in schizophrenia: Advancing our understanding of the phenotype, its neural circuitry and genetic substrates

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1.1. Introduction

In her 1936 report of paired-pulse blink inhibition in 13 Yale undergraduate men, Helen Peak described “quantitative variation in amount of inhibition of the second response incident to changes in intensity of the first stimulus which precedes by different intervals of time” (Peak, 1936). These observations appeared to lay dormant for much of the next 30 years, but there was a resurgence of interest in startle modulation in the 1960's, based primarily on findings from Howard Hoffman's group (e.g. Hoffman and Fleshler, 1963). Almost four decades after Peak's first report, and more than 100 years after prestimulus-induced reflex inhibition was first described by the Russian scientist, Sechenov, Frances Graham summarized the growing literature of weak prestimulation effects on startle magnitude and latency (e.g. Hoffman and Searle, 1968) in her 1974 Presidential Address to the Society for Psychophysiological Research (Graham, 1975; see Ison and Hoffman, (1983) for more historical background). This set the stage for David Braff's 1978 report of findings from Enoch Callaway's laboratory, extending Graham's parametric findings of startle inhibition, and demonstrating a relative loss of prestimulus effects on startle in 12 schizophrenia patients (Braff et al., 1978). Braff and colleagues interpreted this loss to be “consistent with a dysfunction in… early protective mechanisms which would correlate with

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information overload and subsequent cognitive disruption in schizophrenia." They also noted that deficits observed in patients might reflect a range of issues not specific to schizophrenia, including "global psychopathology… stress of hospitalization… [and] antipsychotic medications."

In the 80 years since Peak's systematic studies of blink inhibition, and the 40 years since Braff's published observation of impaired prepulse inhibition (PPI) in schizophrenia patients, PPI has been studied in many thousands of patients, and PPI findings have been reported in approximately 3000 Medline publications. While a relationship between deficient lead stimulus inhibition and "information overload" has not been demonstrated, it is clear from reading the articles in this Special Issue of *Schizophrenia Research* that many other themes of these early studies of startle inhibition – parametric sensitivity, transdiagnostic psychopathology, "trait vs. state" factors including antipsychotic medications and stress – remain critically important to our understanding of the phenomenon of impaired sensorimotor gating in schizophrenia, and its clinical and biological underpinnings. Also represented in this issue is the theme of the genetic regulation of PPI in health and pathology, inspired by promising (though not yet actionable) developments in psychiatric genetics over the past 4 decades.

2.1 The Phenotype

Reduced PPI as a phenotype of schizophrenia has now been reported in several dozen different published studies, conducted in many different laboratories, countries, continents and cultures. We open this Special Issue with an "internal replication" of this finding, from the 5-site Consortium on the Genetics of Schizophrenia (COGS; PI: D. Braff). This report compares PPI across two "waves" of subjects tested over 3.5 years: "Wave 1" consisting of almost 1400 subjects, reported in 2014 (Swerdlow et al., 2014), and "Wave 2" consisting of over 600 new subjects, reported here (Swerdlow et al. 2017). Balancing the added power produced by a 5-site study vs. the added variability associated with multi-site acquisition of a complex phenotype, this report extends themes from Peak (1936), Graham (1975), Braff et al. (1978) and others (Kumari et al., 1999; Swerdlow et al., 2006; Weike et al., 2000) by focusing on the sensitivity of the "PPI phenotype" to startle stimulus parameters, antipsychotic medications and other factors. Cumulatively, these COGS reports represent the largest published sample of PPI in healthy subjects and schizophrenia patients, and significant group differences were detected, with effect sizes ranging from small (d = 0.11) to medium (d = 0.57), depending on specific startle response criteria (e.g. low startle magnitude) and patient characteristics (e.g. sex, smoking, antipsychotic use). Across the many single-site reports of PPI deficits in schizophrenia cohorts, medium effect size differences (approximately d=0.5) indicate that about 69% of schizophrenia patients exhibit PPI levels below the group mean of healthy comparison subjects. While we describe strategies to limit the impact of low reflex magnitude on PPI variability, our current report underscores some limitations of PPI as an experimental measure, as we have discussed elsewhere (Swerdlow et al., 2008, 2014). Specifically, "While these known effects of sex, smoking and medications on PPI can be incorporated statistically into models that test group differences, it is important that they cannot easily be extricated from an individual subject's

PPI value, and thereby complicate the genomic and neurobiological signal provided by this endophenotype."

Despite the challenges in the use of PPI as an endophenotype for multi-site genetic studies, single-site studies continue to report significant PPI deficits in schizophrenia patients. Takahashi and Kamio (2017) review for the first time a list of studies conducted in Japan and China, with a cumulative sample of several hundreds of schizophrenia patients and healthy subjects, demonstrating a consistent pattern of deficient PPI in patients, comparable to what is generally reported in single-site studies from Western countries. Importantly, such cross-cultural confirmation is not as predictable as one might imagine with a basic reflex response, since blink magnitude is modified by features of facial musculature that differ across ethnic groups (Swerdlow et al., 2005), and because there appear to be ethnic differences in the functional impact of polymorphisms thought to moderate PPI (Wang et al. 2013; also see article by Quednow et al. (2017), later in this issue). While complicating moderating factors of both stimulus parameters and medications are discussed, Takahashi and Kamio (2017) clearly make the case that reduced PPI is a "global" schizophrenia phenotype, evident in both predominantly Caucasian Western countries as well as single ethnicity Asian countries.

Another issue raised by Takahashi and Kamio (2017) is the potential utility of PPI and other startle phenotypes in the study of children with Autism Spectrum Disorders (ASDs). While the "jury is still out" on the presence of PPI deficits in ASDs - and Takahashi and Kamio (2017) note the absence of such differences in their Japanese sample – the authors make the important point that reduced PPI is not a phenotype that is specific to schizophrenia. In fact, relatively reduced PPI distinguishes many groups of healthy subjects (e.g. women vs. men; children vs. adults); beyond this, studies have reported that PPI is impaired in patients with OCD (Swerdlow et al., 1993a; Hoenig et al., 2005; Ahmari et al., 2012; Kohl et al., 2015), Tourette Syndrome (Castellanos et al., 1996; Swerdlow et al., 2001b; Zebardast et al., 2013; Castellan Baldan et al., 2014; Buse et al., 2015), Huntington's Disease (Swerdlow et al., 1995; Munoz et al., 2003; Valls-Solé et al., 2004), nocturnal enuresis (Ornitz et al., 1992), Asperger's Syndrome (McAlonan et al., 2002; Howlin and Murphy, 2002), 22q11 Syndrome (Sobin et al., 2005), Kleinfelter Syndrome (Van Rijn et al., 2011), Fragile-X Syndrome (Frankland et al., 2004; Yuhas et al., 2011; Renoux et al., 2014), and blepharospasm (Gomez-Wong et al., 1998). As discussed elsewhere in this issue (e.g. Schwabe and Krauss (2017)), the forebrain regulation of PPI involves interconnected neural circuitry that appears to be relevant to many different disorders, and perhaps particularly relevant to disorders of neurodevelopmental origin. Conceivably, disturbances at any one of several nodes within this circuitry mind produce a "deficient PPI" phenotype, together with a range of different clinical conditions. Perhaps it is equally important to note that sensorimotor gating, as measured by PPI, appears to remain relatively intact, or at least functional, in a number of other serious brain disorders, including attention deficit disorder (ADHD: Castellanos et al., 1996; Ornitz et al., 1992; Ornitz et al., 1999; Conzelmann et al., 2010; Feifel et al., 2009; Hanlon et al., 2009), bipolar disorder (Barrett et al., 2005 (euthymic); Carroll et al., 2007 (manic or mixed episode); but see Sanchez-Morla et al., 2016 and Giakoumaki et al. 2007), and major depressive disorder (Ludewig and Ludewig, 2003; Perry et al., 2004; Quednow et al., 2006), while evidence from chronic substance use disorders is mixed (e.g. Quednow et al., 2004; Schellekens et al., 2012).

The impairment of PPI in psychosis can also be complicated by comorbid disorders; this fact is underscored by Sedwick et al. (2017) in this issue, who report that in a population of violent men in a high-secure forensic psychiatric hospital, with or without psychosis, PPI is impaired among individuals meeting criteria for an antisocial personality disorder (specifically, the ICD-10 classification of Dissocial Personality Disorder (DPD)). This observation is generally consistent with several points raised elsewhere within this issue, i.e. the fact that impaired PPI is not uniquely a function of schizophrenia; that among psychotic patients, other factors (here the presence of a personality disorder in a violent, institutionalized cohort) appear to moderate the expression of reduced PPI; and that early developmental stress (in this case, early psychosocial deprivation, including physical and sexual abuse) may be a strong determinant of the adult PPI phenotype, even independent of the diagnosis of schizophrenia.

Fargotstein et al. (2017) provide the important reminder that PPI is not the only startle reflex parameter that is impaired in schizophrenia patients. They report slowed startle reflex peak latency in their sample of schizophrenia patients -- a common though not ubiquitous finding (see Discussion in Fargotstein et al. (2017)). This phenotype was most pronounced in their subgroup of unmedicated schizophrenia patients, suggesting that - as with PPI in many studies - antipsychotics may partially correct this slow-latency phenotype, or that other factors associated with unmedicated status may also contribute to prolonged reflex latency. Importantly, in this report as in many others, latency *facilitation* – the normal reduction in reflex latency on prepulse+pulse trials - was intact in patients, including those who were unmedicated. This intact form of prepulse modification of startle suggests that even unmedicated patients are “processing” the prepulse – i.e. it is altering brain function by “speeding up” the reflex – and yet the prepulse is *not normally inhibiting reflex magnitude* (in Fargotstein et al., this PPI deficit was detected only among unmedicated patients). In this way, the presence of intact latency facilitation, together with impaired magnitude suppression (PPI), argues *against* a generalized failure of reflex modification in schizophrenia, and *for* a more specific deficit of PPI. Fargotstein and colleagues also point out the high heritability of startle latency, its potential value in predicting conversion to psychosis and its association with specific genes thought to confer risk for schizophrenia. These facts, together with the very low variance evident in measures of reflex latency, argue for its utility as a schizophrenia endophentype.

3.1 Neural Circuitry

Another important theme in this Special Issue is that – as much, or more, than most other complex human neurobehavioral phenomenon - the biology of sensorimotor gating, measured operationally by PPI, has been elucidated by convergent findings from human and infrahuman studies. Rodent studies of lead stimulus modification of startle by Howard Hoffman, Jim Ison and others were heavily cited in Fran Graham's 1974 SPR Presidential Address as foundational for the evolving human startle literature. Animal studies first linked Braff's observation of deficient PPI to an anatomical (ventral striatum) and neurochemical (DA) substrate (Sorenson and Swerdlow, 1982; Swerdlow et al., 1986), and subsequent reports centered these substrates within an extended forebrain and pontine circuit that regulates PPI in rodents (e.g. Koch and Schnitzler, 1997; Swerdlow et al., 1992, 1993c).

Many of the key nodes within the rodent-based cortico-striato-pallido-pontine (CSPP) and cortico-striato-pallido-thalamic (CSPT) PPI-regulatory circuitry have been at least loosely extrapolated to humans, based on evidence for PPI deficits in patient populations with known or suspected localized circuit pathology, as well as supportive brain imaging studies (cf. Swerdlow and Koob, 1987; Swerdlow et al., 1993b, 1995b, 2001b; Schwabe and Krauss (2017), this issue). Findings implicating white matter pathology in disorders associated with deficient PPI suggest that disturbances in either CSPT “nodes” or their interconnections may contribute to reductions in sensorimotor gating. Several reports in this Special Issue underscore the continued importance of studies in laboratory animals to our evolving understanding of PPI and its neural and genetic substrates.

Two reports in this issue use rodent models to further advance our understanding of the neurobiology of PPI, with particular relevance to limbic CSPP and CSPT circuitry associated with schizophrenia. Ma and Leung (2017) summarize an impressive body of work, mostly generated by their group, implicating the hippocampus and its interconnections with the medial septum and nucleus accumbens in NMDA antagonist-induced deficits in measures relevant to auditory information processing – particularly PPI, gating of auditory evoked potentials and spontaneous gamma oscillations. Interestingly, a more global role for hypoglutamatergic function in deficient PPI in humans is more difficult to reconcile with the PPI-*enhancing* effects of NMDA antagonists, including ketamine (Duncan et al., 2001; Abel et al., 2003), memantine (Swerdlow et al., 2009) and amantadine (Swerdlow et al., 2002) in healthy adults, and in the case of memantine, in schizophrenia patients (Swerdlow et al., 2016). A hippocampal role in the regulation of PPI has been suggested since studies by Caine et al. (1991, 1992), and the importance to psychosis of epileptiform discharges in hippocampal-accumbens projects has been discussed since Janice Stevens' landmark 1973 paper, “An Anatomy of Schizophrenia?”. Ma and Leung advance the science substantially by proposing a detailed intrinsic hippocampal circuit model to account for their neurophysiological and behavioral findings after pharmacologic and electrical manipulations, and more generally, for “distorted sensory integration, and impaired cognitive and memory processing” in schizophrenia.

Schwabe and Krauss (2017) describe another impressive body of work, in which they utilize deep brain stimulation (DBS) in rodents to map CSPT circuits that regulate PPI, and by extension, to explore DBS sites that might be used to normalize sensorimotor gating as a therapeutic target for schizophrenia, obsessive compulsive disorder (OCD) and Tourette Syndrome (TS). They identify stimulation and lesion sites within rodent equivalents to human pallidal and thalamic subregions – which have been clinically effective as DBS sites for TS and other disorders - that normalize rodent PPI after drug-induced deficits and enhance PPI in rodents who normally express low levels of PPI. In models of particular relevance to schizophrenia, discussed later in this issue by Khan and Powell (2017), PPI deficits after maternal immune activation are normalized by high frequency stimulation of the medial prefrontal cortex (mPFC), nucleus accumbens (NAC), globus pallidus (GP) and mediodorsal thalamus (MD). They also describe the role for many of these CSPT circuit nodes in the normal regulation of PPI in intact rats, consistent with the proposed role of this circuitry in the regulation of sensorimotor gating in non-pathological states. Lastly, they describe more recent studies showing normalizing effects of DBS on both impaired PPI and

symptoms in OCD, and the unique potential for “mapping” the human regulation of PPI via studies using DBS in several brain regions across different patient populations.

4.1 Genes and Environment

A major “paradigm shift” in the science of sensorimotor gating in the new millennium is the use of PPI as a potential “endophenotype”, in studies of PPI genetics, and in the search for schizophrenia risk genes. The notion that a single gene might have a robust impact on a complex phenotype like PPI seems quite believable, when one considers that PPI is strongly reduced in patients with Huntington's Disease (Swerdlow et al., 1995; Munoz et al., 2003; Valls-Solé et al., 2004) and in transgenic rodents models of this disorder (Carter et al., 1999). Many studies have assessed the association of PPI with suspected schizophrenia-linked single nucleotide polymorphisms (SNPs), and while promising findings have been reported with many SNPs, such studies carry a substantial propensity for false positive and negative findings. In this issue, Quednow et al. (2017) report the first meta-analysis of PPI SNP findings from 16 independent samples with 2660 subjects and 43 SNPs. Four SNP associations were promising – COMT rs4680, GRIK3 rs1027599, TCF4 rs9960767 and PRODH rs385440 – with effect sizes ranging from 0.19 – 0.28. Importantly, each of these genotypes or closely connected genes have been linked to either the neurobiology of PPI, schizophrenia (or the related 22q11 deletion syndrome), or both, providing convergent support for these meta-analytic findings. The authors identify factors that may complicate the interpretation of these results, including sex differences in the observed PPI-rs4680 association, the potentially confounding association of GRIK3 with startle magnitude, and the difficulty harmonizing data across studies using different stimulus parameters, study samples (medicated vs. unmedicated patients vs. healthy subjects), etc. Nonetheless, these findings provide some robust clues regarding genes that appear to regulate PPI, and conceivably, contribute to reductions in PPI in schizophrenia and other neurodevelopmental disorders.

Van den Buuse et al. (2017) describe another strategy for investigating the role of specific schizophrenia-implicated SNPs in the regulation of PPI, via the use of humanized BDNF “knock-in” mice, designed to carry the three possible combinations of the Val66Met BDNF SNP. Importantly, their findings focus on the impact of these 3 SNP configurations not on basal PPI per se, but instead on the “disruptability” of PPI in response to dopamine agonists and NMDA antagonists (similar to a strategy using rat strains with distinct regional gene expression patters (Shilling et al., 2008)), and on the sensitivity to early life cortisone exposure, testing a “stress diathesis” model of deleterious effects of stress hormones in genetically susceptible individuals. BDNF “Val/Val” mice were resistant to the PPI-disruptive effects of apomorphine (but not MK-801), and this Val/Val “protection” of PPI was prevented by chronic CORT exposure. These findings provide a clear example of one of many likely “gene × environment” (G×E) interactions that regulate PPI, and demonstrate how genes can potently moderate the “disruptability” of PPI and yet potentially be “invisible” to simple association studies that do not include a drug- or developmental “provocation”.

Finally, the theme of G×E and E×E interactions in the “low PPI” phenotype is discussed in depth in Khan and Powell's (2017) paper on PPI in “2-hit” models of schizophrenia risk factors. Here they review the interaction of genetic and environmental experimental manipulations in the genesis of impaired PPI in animal models, as an approach to evaluating models of schizophrenia risk factors. In essence, reduced PPI is used as a target phenotype, and its production by interacting factors (e.g. mouse DISC1 mutants and maternal immune activation (Lipina et al., 2001e.g. mouse DISC1 mutants and maternal immune activation (Lipina et al., 2012) provides a form of validation that such factors might contribute to deficient PPI in schizophrenia patients. The authors review a long list of interacting “2-hit” genetic and environmental factors that result in the development of PPI deficits in laboratory animals, underscoring the fact that the low PPI phenotype can be a function of many different pathways, presumably converging on a shared underlying neural circuitry; the utility of such models extends beyond tests of potential etiologies, and also includes therapeutic trials that might potentially identify novel interventions that prevent specific 2-hit effect on PPI.

5.1 Conclusion

Since the initial report of deficits in 12 SZ patients four decades ago, PPI has provided essential insights into the nature of SZ and related neuropsychiatric disorders. From these modest beginnings, PPI has been productively studied in thousands of patients and translational studies that have revealed the complex genomic and neural substrates underlying sensorimotor gating. This special issue of *Schizophrenia Research* profiles our rapidly expanding knowledge base via contributions from investigators around the world. These papers demonstrate that PPI can be reliably and validly measured in large-scale multi-site consortium studies of healthy and SZ patients and that participant characteristics including sex, medications, smoking, genes, early life environment, and other interacting variables “matter.” Despite substantial heterogeneity in these critical domains, reduced PPI nonetheless appears to be a global SZ-related phenotype; deficits are not, however, unique to SZ but likely a function of disturbances within interconnected forebrain circuitry of relevance to many neurodevelopmental and neuropsychiatric disorders.

The application of PPI as an endophenotype in neuropsychiatry belies the fact that this measure is malleable in both humans and laboratory animals. Rodent studies continue to elucidate the role of CSPT circuitry for regulating normal and reduced PPI with elegant demonstrations that drug-, lesion-, and maternal immune activation-induced PPI deficits can be reversed via stimulation at several nodes within the circuitry. Such knowledge highlights many future “pathways” for developing new SZ treatments rather than the single mechanistic “smoking gun” that has eluded our field. Importantly, PPI is but one of many translational measures that has transformed our understanding of SZ over the past 4 decades. The present collection of findings supports the sustained optimism for using PPI and other translational biomarkers to accelerate the pace of development of more targeted CNS therapeutics that can improve the outcomes of patients in the years to come.

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